

JUL 29 1998

FREEDOM OF INFORMATION SUMMARY

Combined use of MONTEBAN[®], BMD[®], and 3-NITRO[®] in Chicken Feeds

I. GENERAL INFORMATION:

NADA: 140-852

Sponsor: Alpharma Inc.
One Executive Drive
Fort Lee, NJ 07024

Generic Names: Narasin
Bacitracin methylene disalicylate
Roxarsone

Trade Names: MONTEBAN[®]
BMD[®]
3-NITRO[®]

Marketing Status: OTC

(Note: This supplement provides for two new claims as described in section II)

II. INDICATIONS FOR USE:

- 1) For prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.
- 2) For prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

III. DOSAGE:

A. Dosage form: This supplemental NADA provides for the combined use of these three Type A medicated articles: narasin as per 21 CFR § 558.363, bacitracin methylene disalicylate as per 21 CFR § 558.76, and roxarsone as per 21 CFR § 558.530. Narasin is supplied as Type A medicated articles in concentrations of 36, 45, 54, 72, or 90 grams narasin activity per pound. Bacitracin methylene disalicylate is supplied as Type A medicated articles in concentrations of 10, 25, 30, 40, 50, 60, or 75 grams bacitracin activity per pound. Roxarsone is supplied as Type A medicated articles in concentrations of 45.4, 90, or 227 grams of roxarsone activity per pound.

NADA 140-852

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B. Route of Administration: Oral, *via* the feed.

C. Recommended Dosage:

Narasin
Narasin is added to broiler chicken feed at concentrations from 54 to 72 g/ton for prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati* and *E. maxima*.

Bacitracin methylene disalicylate
1) Bacitracin methylene disalicylate is added to broiler chicken feed at a concentration of 50 g/ton as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin.

2) Bacitracin methylene disalicylate is added to broiler chicken feed at a concentration of 100 to 200 g/ton as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin.

Roxarsone
Roxarsone is added to broiler chicken feed at concentrations from 22.7 to 45.4 g/ton for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

CAUTION (1): For broiler chickens only. Do not feed to laying hens. Do not allow adult turkeys, horses, or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis.

CAUTION (2): For broiler chickens only. Do not feed to laying hens. Do not allow adult turkeys, horses, or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water intake may result in leg weakness or paralysis. To control a necrotic enteritis outbreak, start medication at the first clinical signs of disease. The dosage range permitted provides for different levels based on severity of the infection. Consult a poultry diagnostic laboratory or pathologist to determine the diagnosis and advice regarding the optimal level of drug. Administer continuously for 5-7 days or as long as clinical signs persist, and then reduce medication to prevention level (50 g/ton bacitracin methylene disalicylate).

IV. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC §512(d)(4)(D)).

Narasin, as provided by Elanco Animal Health, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* (21 CFR §558.363 (c)(1)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in feed for broiler chickens as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR §558.95 (d)(1)(vi) and (d)(1)(ix), respectively). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing chickens for increased rate of weight gain, improved feed efficiency and improved pigmentation (21 CFR §558.530 (d)(1)). Effectiveness for each drug, bacitracin methylene disalicylate, roxarsone, and narasin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 46-592 and 7-891, and in approved NADA 118-980, respectively, to which Alpharma Inc. has a right of reference.

Since narasin, bacitracin methylene disalicylate, and roxarsone each have at least one use that is different from all other animal drugs used in the combination, the NADA must demonstrate that narasin plus roxarsone plus bacitracin methylene disalicylate provide appropriate concurrent use for the intended target population. The use of narasin plus bacitracin methylene disalicylate plus roxarsone provides appropriate concurrent use because these drugs are intended to treat different conditions (narasin, coccidiosis; bacitracin methylene disalicylate, necrotic enteritis; roxarsone, pigmentation problems) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. Narasin is not considered to be an antibacterial animal drug for use in broiler

chickens for the purposes of 512(d)(4) of the FFDCA, because narasin is approved only for prevention of a protozoal disease in broiler chickens. Roxarsone is not considered to be an antibacterial animal drug for use in broiler chickens for the purposes of 512(d)(4) of the FFDCA, because roxarsone is not approved for use in broiler chickens for the diagnosis, cure, mitigation, treatment or prevention of bacterial disease and is not approved for any other use the Center for Veterinary Medicine deems attributable to its antibacterial properties.

V. ANIMAL SAFETY

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

Narasin, as provided by Elanco Animal Health, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* (21 CFR §558.363 (c)(1)(i)). Bacitracin methylene disalicylate, as provided by Alpharma Inc., has previously been separately approved for use in feed for broiler chickens as an aid in the **prevention** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and as an aid in the **control** of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin (21 CFR §558.95 (d)(1)(vi) and (d)(1)(ix), respectively). Roxarsone, as provided by Alpharma Inc., has previously been separately approved for use in feed for growing chickens for increased rate of weight gain, improved feed efficiency and improved pigmentation (21 CFR §558.530 (d)(1)). Target animal safety for each drug, bacitracin methylene disalicylate, narasin, and roxarsone, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Alpharma Inc.'s approved NADAs 46-592 and 7-891, and in approved NADA 118-980, respectively, to which Alpharma Inc. has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of narasin, bacitracin methylene disalicylate, or roxarsone when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study(ies) are required for approval of NADA 140-852.

VI. HUMAN SAFETY:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

Non-interference among the active ingredients (narasin, bacitracin methylene disalicylate, and roxarsone) in tissue residue depletion at the longest withdrawal time (5 days) or in the performance of the analytical methods for tissue residues was demonstrated in the FOI Summary for the original approval of this combination.

VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that narasin (54 to 72 g/ton) plus bacitracin methylene disalicylate (50 g/ton, or 100 to 200 g/ton) plus roxarsone (22.7 to 45.4 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary.

Pursuant to 21 CFR §514.106 (b)(2)(vi), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Residue data show that narasin is within the established safe concentrations in edible chicken tissues (0.6 ppm in muscle; 1.8 ppm in liver; 1.2 ppm in skin and fat). Residue data show that roxarsone (as residues of arsenic in edible tissues of chickens) is well below the tolerances of 0.5 ppm arsenic in muscle and 2.0 ppm arsenic in edible chicken by-products.

Attached labeling: Type C medicated Feed (Blue Bird)

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cc: HFV-199 NADA 140-852, C0007, S0008, and S0009 Orig.
HFV-2 Special Mailing List
HFV-12 FOI Staff
HFV-102 GADQC Reserve Copy
HFV-102 Green Book (NTurner)
HFA-305 Dockets Management Branch
HFR-MA350 NWJ-DO
JMGilbert/HFV-128:07/13/97

ec: CVM Records\ONADE\N140852\C0007FOI.SUM

Lot No. _____

NET WEIGHT ON BAG OR BULK

**BLUE BIRD NARASIN/BMD/ROXARSONE-- PNE
TYPE C BROILER FEED
MEDICATED**

For prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENTS

Narasin 54 to 72 g/ton
Bacitracin methylene disalicylate..... 50 g/ton
Roxarsone..... 22.7 to 45.4g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than %
Crude Fat, not less than..... %
Crude Fiber, not more than..... %

INGREDIENTS

Each ingredient must be specifically named (unless stated as such in the guaranteed analysis listing) in accordance with the names and definitions listed in Title 21 CFR 501.110.

DIRECTIONS FOR USE

Feed continuously as the sole ration.

WARNING: Withdraw 5 days before slaughter.

CAUTION: For broiler chickens only. Do not feed to laying chickens. Do not allow adult turkeys, horses or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water may result in leg weakness.

**BLUE BIRD FEED MILL
Any Town, USA 12345**

Lot No. _____

NET WEIGHT ON BAG OR BULK

**BLUE BIRD NARASIN/BMD/ROXARSONE-- CNE
TYPE C BROILER FEED
MEDICATED**

For prevention of coccidiosis caused by *Eimeria necatrix*, *E. tenella*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, as an aid in control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broiler chickens.

ACTIVE DRUG INGREDIENTS

Narasin 54 to 72 g/ton
Bacitracin methylene disalicylate 100 to 200 g/ton
Roxarsone 22.7 to 45.4g/ton

GUARANTEED ANALYSIS

Crude Protein, not less than %
Crude Fat, not less than %
Crude Fiber, not more than %

INGREDIENTS

Each ingredient must be specifically named (unless stated as such in the guaranteed analysis listing) in accordance with the names and definitions listed in Title 21 CFR 501.110.

DIRECTIONS FOR USE

Feed continuously as the sole ration.

WARNING: Withdraw 5 days before slaughter.

CAUTION: For broiler chickens only. Do not feed to laying chickens. Do not allow adult turkeys, horses or other equines access to formulations containing narasin. Ingestion of narasin by these species has been fatal. Use as the sole source of organic arsenic. Poultry should have access to drinking water at all times. Drug overdosage or lack of water may result in leg weakness. To control a necrotic enteritis outbreak, start medication at the first clinical signs of disease. The dosage range permitted provides for different levels based on severity of the infection. Consult a poultry diagnostic laboratory or pathologist to determine the diagnosis and advice regarding the optimal level of drug. Administer continuously for 5-7 days or as long as clinical signs persist, and then reduce medication to prevention level (50 g/ton bacitracin methylene disalicylate).

BLUE BIRD FEED MILL
Any Town, USA 12345